

WHAT IS CLAIMED IS:

- 1       1. A method for identifying a test composition or agent which modulates the  
2       efficiency of translation termination which comprises:
  - 3       (a)     contacting the MTT1 with a test composition or agent under conditions  
4       permitting binding between the MTT1 and the test composition;
  - 5       (b)     detecting specific binding of the a test composition or agent to the MTT1;  
6       and
  - 7       (c)     determining whether the a test composition or agent inhibits the MTT1 so  
8       as to identify a test composition or agent which is which modulates the  
9       efficiency of translation termination.
  
- 1       2. A method of identifying a test composition or agent which modulates binding to  
2       *MTT1*, the method comprising:
  - 3       (a)     incubating components comprising the test composition, and *MTT1*  
4       wherein the incubating is carried out under conditions sufficient to permit  
5       the components to interact; and
  - 6       (b)     measuring the effect of the test composition on the binding to *MTT1*.
  
- 1       3. The method of claim 2, further comprising identifying a gene comprising;
  - 2       (a)     introducing into a cell a test composition which modulates  
3       binding to *MTT1*;
  - 4       (b)     determining the phenotype of the cell after (a);
  - 5       (c)     comparing the cellular phenotype after (a) with the cellular phenotype  
6       before (a); and
  - 7       (d)     identifying the gene of the cell into which the test composition has been  
8       introduced.

- 1 4. A method of detecting a nonsense suppression disorder associated with the  
2 expression of mtt1 protein, wherein the method comprises contacting a sample  
3 from a subject having or suspected of having a disorder with a reagent that detects  
4 expression of the mtt1 protein and detecting the binding of the reagent in the  
5 sample.
- 1 5. An agent which inhibits, facilitates, or modulates the helicase, ATPase activity  
2 of MTT1.
- 1 6. The agent of claim 5, wherein the agent is a ribozyme, antisense molecule, or  
2 ligand which acts as an antagonist or agonist of translation termination.
- 1 7. An isolated multiprotein complex comprising a MTT1 gene, human Upf1p  
2 protein, a peptidyl eucaryotic release factor 1 (eRF1) and a peptidyl eucaryotic  
3 release factor 3 (eRF3), wherein the complex is effective to modulate peptidyl  
4 transferase activity during translation.
- 1 8. The complex of claim 7, further comprising human Upf3p and/or Upf2p.
- 1 9. An antibody which binds to the complex of claim 7.
- 1 10. The antibody of claim 9, wherein the antibody is a monoclonal or polyclonal
- 1 11. The antibody of claim 9, wherein the antibody has a label.
- 1 12. An agent which binds to the complex of claims 7 or 8.
- 1 13. An agent which inhibits or modulates the binding of human MTT1 to eRF3; or  
2 MTT1 to a polysome.

- 1        14. An agent which facilitates the binding of human MTT1 to eRF3; or MTT1 to a  
2        polysome.
- 1        15. The agent of claim 12, wherein the agent has a label or marker.
- 1        16. The agent of claim 14, wherein the agent is an antisense molecule or a ribozyme.
- 1        17. A method of modulating peptidyl transferase activity during translation,  
2        comprising contacting a cell with the complex of claim 7 in an amount effective  
3        to facilitate translation termination, thereby modulating the peptidyl transferase  
4        activity.
- 1        18. A method of modulating peptidyl transferase activity during translation,  
2        comprising contacting a cell with the agent of claim 12, in an amount effective  
3        to suppress nonsense translation termination, thereby modulating the peptidyl  
4        transferase activity.
- 1        19. The method of claim 18, wherein the peptidyl transferase activity during  
2        translation comprises initiation, elongation, termination and degradation of  
3        mRNA.
- 1        20. A method of modulating the efficiency of translation termination of mRNA at a  
2        nonsense codon and/or promoting degradation of aberrant transcripts,  
3        comprising contacting a cell with the agent of claim 12, in an amount effective  
4        to modulate the efficiency of translation termination of mRNA at a nonsense  
5        codon and/or promoting degradation of aberrant transcripts.
- 1        21. A method of screening for a drug involved in peptidyl transferase activity during  
2        translation comprising: a) contacting cells with a candidate drug; and b) assaying

3 for modulation of the complex of claims 7, wherein a drug that modulates  
4 complex is involved in peptidyl transferase activity.

1 22. A method of screening for a drug active involved in enhancing translation  
2 termination comprising: a) contacting cells with a candidate drug; and b)  
3 assaying for modulation of the protein complex of claims 7; wherein a drug that  
4 modulates protein complex is involved in enhancing translation termination.

1 23. A method of screening for a drug involved in enhancing translation termination  
2 comprising: a) incubating the drug and the complex; and b) measuring the effect  
3 on nonsense suppression, thereby screening for a drug involved in enhancing  
4 translation termination.

1 24. The method of claim 23, wherein the assay is a RNA assay or a ATPase assay.

1 25. A method of screening for a drug which inhibits the interaction between MTT1  
2 and eRF3, comprising: a) contacting cells with a candidate drug; and b) assaying  
3 for modulation of the complex of claim 7, wherein a drug that modulates the  
4 binding of MTT1 to eRF3 is involved in enhancing translation termination.

1 26. A method of modulating the efficiency of translation termination of mRNA  
2 and/or degradation of aberrant transcripts in a cell, said method comprising: a)  
3 providing a cell containing a vector comprising the nucleic acid encoding the  
4 complex of claim 7; or an antisense thereof; b) overexpressing said vector in  
5 said cell to produce an overexpressed complex so as to interfere with the  
6 function of the complex.

1 27. A method for identifying a disease state involving a defect in the complex of  
2 claim 7 comprising: (a) transfecting a cell with a nucleic acid which encodes the  
3 complex; (b) determining the proportion of the defective complex of the cell after

4 transfection; (c) comparing the proportion of the defective complex of the cell  
5 after transfection with the proportion of defective complex of the cell before  
6 transfection.

1 28. A method for treating a disease associated with peptidyl transferase activity,  
2 comprising administering to a subject a therapeutically effective amount of a  
3 pharmaceutical composition comprising the complex of claim 7 or the agent of  
4 claim 12, and a pharmaceutical carrier or diluent, thereby treating the subject.

1 29. The method of claim 28, wherein the disease results from a nonsense or  
2 frameshift mutation.

1 30. The method of claim 29, wherein the disease is  $\beta$ -thalassemia,  $\beta$ -globin,  
2 Duchenne/Becker Muscular Dystrophy, Hemophilia A, Hemophilia B, Von  
3 Willebrand Disease, Osteogenesis Imperfecta (OI), Breast cancer, Ovarian  
4 Cancer, Wilms Tumor, Hirschsprung disease, Cystic fibrosis, Kidney Stones,  
5 Familial hypercholesterolemia (FH), Retinitis Pigmentosa, or  
6 Neurofibromatosis, Retinoblastoma, ATM, Costmann Disease.

1 31. A method for identifying a disease state involving defective multimeric proteins  
2 comprising:

- 3 (a) transfecting a cell with the vector of claim ;  
4 (b) determining the proportion of defective multimeric proteins of the cell  
5 after transfection;  
6 (c) comparing the proportion of defective multimeric proteins of the cell after  
7 transfection with the proportion of defective multimeric proteins of the  
8 cell before transfection.

1 32. A method of identifying genes which are involved in modulation of translation  
2 termination, which comprises: a) isolated a gene of interest; and b) determining

3           whether the gene of interest comprises motifs I-IX, wherein if the gene comprises  
4           any one of the nine motifs the gene modulates translation fidelity including  
5           iniatiatioin, elongation, termination, termination, decay.

1           33. The method of claim 32, wherein the motif I comprises the sequence:  
2           GppGTKTxT-X(n).

1           34. The method of claim 32, wherein the motif II comprises the sequence  
2           riLxcaSNxAxDxI-X(n).

1           35. The method of claim 32, wherein the motif III comprises the sequence  
2           vviDExxQaxxxxxxiPi- X(n).

1           36. The method of claim 32, wherein the motif IV comprises the sequence xxil  
2           aGDxxQLp- X(n).

1           37. The method of claim 32, wherein the motif V comprises the sequence lxx SLF  
2           erv- X(n).

1           38. The method of claim 32, wherein the motif VI comprises the sequence  
2           LxxQYRMhpxisefpxYxgxL- X(n).

1           39. The method of claim 32, wherein the motif VII comprises the sequence  
2           IgvitPYxxQvxxl- X(n).

1           40. The method of claim 32, wherein the motif VIII comprises the sequence  
2           vevxtVDxFQGreKdxliIsc VR- X(n).

- 1 41. The method of claim 32, wherein the motif IX comprises the sequence
- 2 iGFLxdxRRINValTRak.